Chromosome Dynamics: Actin's Gone Fishing

Chromosome congression and segregation have been widely known to be coordinated by the function of the dynamic spindle microtubules. But recent work suggests that oocytes may employ a unique actin-dependent mechanism of chromosome delivery to the spindle.

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Proper chromosome segregation is a critical event that determines the fate of the cell and ultimately that of the whole organism. Failure of chromosomes to segregate properly during meiosis is a major cause of birth defects, and missegregation of chromosomes in somatic cells is a hallmark of cancer. During this 'chromosome dance', chromosomes congress toward the spindle equator, align at the metaphase plate and are segregated into the two daughter cells. While microtubules are known to be the major coordinators of chromosome congression and segregation, Lenart *et al.* [1] have recently discovered a unique actin-dependent mechanism for chromosome movement in oocytes.

Although the involvement of actin in chromosome behavior has been postulated for several years [2,3], the work of Lenart *et al.* [1] is the first to demonstrate the mechanism by which actin functions. Their new work shows that actin forms a fishnet-like structure, which collects the dispersed chromosomes and contracts, bringing the chromosomes in close proximity with the microtubules of the forming spindle. This finding adds a new and exciting dimension to our view of cell division.

During the conventional 'search and capture' model for chromosome congression, the dynamic spindle microtubules grow and shrink searching three-dimensional space, until they eventually capture chromosomes [4]. Recent modeling studies [5], however, suggest that 'search and capture' alone may not be sufficient to capture all chromosomes on a typical vertebrate spindle in a time-frame consistent with the observed chromosome congression times. This becomes a critical problem in the starfish oocyte nucleus because of its large size. The scattered chromosomes at nuclear envelope breakdown (NEBD) are simply too far from the dynamic microtubules of the forming spindle to allow for the connections to be made. The microtubules have a maximal length of only 15–20 μm, while the oocyte nucleus is roughly 80 μm in diameter [6]. These geometrical problems stimulated scientists to discover how chromosome–microtubule interactions are established in this system.

In an elegant set of experiments using cutting-edge imaging technology, Lenart *et al.* [1] found that microtubules are not sufficient for controlling chromosome congression following NEBD, and obtained compelling evidence that actin is required to bring chromosomes to the spindle in the starfish oocyte [1]. Immediately after NEBD, chromosomes move slowly (~3 μm min^{-1}) toward the animal pole without any obvious contact with microtubules. Treatment of the oocytes with nocodazole, a drug that induces microtubule depolymerization, had no effect on the ability of chromosomes to migrate toward the centrosomes. But treatment of cells with latrunculin B, which depolymerizes actin, caused a significant decrease in the slow migration of chromosomes toward the centrosomes, which resulted in an increased percentage of oocytes with 'lost' chromosomes. Interestingly, after being brought to the vicinity of the forming spindle, chromosomes switched to a faster movement (>12 μm min^{-1}), which was disrupted by the addition of nocodazole but not latrunculin B [1].

Together, these findings suggest that actin is responsible for chromosome migration toward the spindle, and that microtubules play a more critical role in the final congression and alignment of chromosomes on the spindle itself. Furthermore, it appears that in the oocyte, there is a cytoskeletal flip-flop in which microtubules, which are traditionally thought of as being

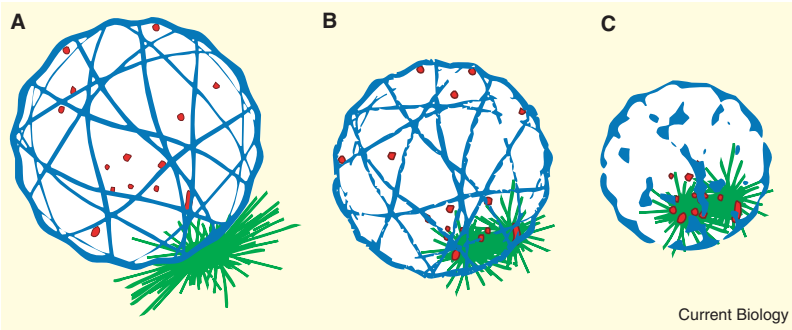

Figure 1. Actin is required for chromosome delivery in the starfish oocyte.

(A) At the onset of meiosis, actin (blue) forms long 'fishnet-like' polymers surrounding the nucleus, while the spindle microtubules (green) form their bipolar structure, and the chromosomes (red) are scattered in the nucleus. (B) The actin network starts to contract, which brings the chromosomes towards the site of the microtubules. (C) When the chromosomes have reached the vicinity of the dynamic microtubules, 'search and capture' ensues to align chromosomes on the spindle as the actin continues to depolymerize.

required for long-range intracellular movements, are used for short-range movements, and actin, traditionally thought to be used for short-range movements, is now on the long-range haul [7].

How does actin actually move the chromosomes? Live imaging of F-actin shows that it forms a fishnet structure surrounding the oocyte nucleus, which contracts over time and collects the scattered chromosomes within close proximity to the spindle microtubules (Figure 1). This polymerization of actin occurs in concert with NEBD at the rim of the nucleus, directly under the nuclear envelope. Interestingly, actin polymerization depletes the nuclear pool of actin, whose precise role remains unclear [8,9]. It is possible that chromosome migration is one function for nuclear actin.

To examine how actin dynamics are involved in the migration of chromosomes to the spindle, Lenart *et al.* [1] treated oocytes with the drugs phalloidin and jasplakinolide, which are known to stabilize actin filaments [10]. Treatment of the oocytes with either drug caused chromosome-loss defects similar to what had been observed with latrunculin B. These results suggest that a static actin filament network is not sufficient to drive chromosome movement, but rather a dynamic actin network is necessary.

The proposed mechanism is that the actin fishnet must depolymerize and contract, thus delivering chromosomes to the spindle. It is now essential to elucidate the dynamics of actin within this network to fully understand how it functions. While technically difficult, it should be possible to use fluorescence recovery after photobleaching or fluorescent speckle microscopy [11], where the dynamics of actin polymerization and depolymerization as well as its movement and organization can be explored. It will also be critical to identify the key molecular regulators of the actin dynamics that are critical for chromosome migration.

One particularly intriguing finding was that injection of plasmid-coated DNA beads into the oocyte induced the assembly of actin patches around the beads similar to the actin patches that had been observed around the chromosomes in their imaging experiments [1]. This approach is analogous to studies utilizing *Xenopus* egg extracts in which chromatin-coated magnetic beads initiate spindle formation in the extracts [12]. Normally, during preparation of these meiotic extracts, cytochalasin B is added to depolymerize actin. It would be interesting to observe what happens to chromosomes if the actin is left intact and how this could affect the behavior of the chromosomes. The *Xenopus* extract system additionally provides a cell-free environment that would be particularly powerful for further analysis of how actin and chromatin interact, similar to the way in which the system has been exploited to study the mechanisms of spindle assembly [13,14].

While the new findings [1] do not necessarily change our view of the importance of microtubules in spindle assembly and chromosome dynamics, they add another exciting dimension to our knowledge of this process. They illustrate a distinct and novel mechanism of function of actin in chromosome migration to the spindle and highlight the overall importance of the cytoskeleton network.

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DOI: 10.1016/j.cub.2005.10.004